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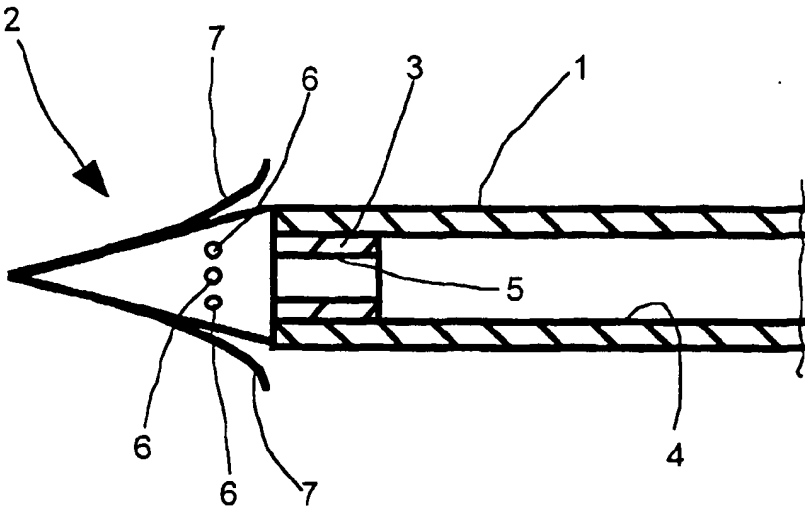
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,*

[Continued on next page]

(54) Title: METHOD AND MEANS FOR LOCATING AND SIGNALLING A NON-PALPABLE LESION IN SOFT TISSUES



(57) Abstract: A method for identifying and indicating a non-palpable lesion in soft tissue comprises injecting marker means into said tissue via a hollow needle along a route leafing to said lesion, said marker means comprising a macromolecular substance detectable by echography or magnetic resonance. Means for identifying and indicating a non-palpable lesion in soft tissue comprise marker means injectable into said soft tissue along a route leading to said lesion, said marker means comprising a macromolecular substance detectable by echography or magnetic resonance. Means for identifying and indicating a non-palpable lesion in soft tissue comprise needle means with a hollow cylindrical body (1) and a tip (2) releasably fixed to an end of said body (1) and provided with fixing means (7) suitable for fixing into said soft tissue.

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Method and means for locating and signalling a non-palpable lesion in soft tissues

The present invention relates to a method and means for identifying and indicating lesions in soft tissue, in particular non-palpable breast lesions.

From prior art it is known identifying and indicating non-palpable lesions in soft tissue by inserting a cannula needle, i.e. a hollow needle, into the tissue and identifying the position of the needle through known display techniques such as mammography, radiography, etc. When the needle has reached the lesion a metal wire is fed through the needle until the wire reaches the previously identified lesion and the metal wire is left in position whereas the cannula needle is extracted, whereby the wire is a reference for a surgeon, who must then operate on the lesion. The end of the wire in contact with the identified lesion generally has fixing means which remain fixed to the tissue in the zone of said lesion.

This system has the drawback that the wire may break or be moved due to movements of the patient's body which cause the tissue to move in the zone in which the wire was inserted thus making said wire useless as a reference. Moreover, the metal wire inside the soft tissue may be made visible by mammography but cannot be detected by other types of examination such as echography or magnetic resonance. This makes the use of the metal wire as a reference not very versatile.

Moreover, the metal wire is disagreeable to the patient and for this reason it can be left in position only for short periods; the metal wire therefore has to be inserted only shortly before a surgical intervention.

Another system used to indicate a lesion identified in soft tissue provides progressively extracting a hollow needle and simultaneously injecting a preparation containing sterile carbon, after identification of the lesion and positioning of a hollow needle with its tip in the lesion. The sterile carbon

injected along the needle route as far as the identified lesion helps the surgeon to more easily visually identify the route to follow to surgically reach said lesion.

Marking with sterile carbon has the advantage of remaining for a long time and of not causing the patient discomfort, so that it can be carried out considerably in advance of the surgeon's intervention.

However, marking with active carbon is visible only to the naked eye and cannot be detected through imaging methods such as mammography, echography, magnetic resonance, etc. Moreover, when active carbon is injected great care has to be taken to inject it uniformly, whilst the cannula needle is being withdrawn, to avoid the risk that a major portion of the route of the cannula needle is not marked with the active carbon, which would make the marking substantially unusable.

From prior art it is also known using, instead of active carbon, radiological contrast means such as Tecnezio. However, this system involves numerous organisational problems inasmuch as Technezio has to be injected shortly before the surgical intervention and also requires close coordination between the department of Nuclear Medicine and the departments of Radiology and Surgery. This system cannot therefore be used if a certain time, for example, a few days, must elapse between marking and the surgical intervention. Moreover, Tecnezio marking can be detected only by an appropriate probe but cannot be seen with the naked eye or with imaging methods.

The object of the present invention is to provide a method and means for identifying non-palpable lesions in soft tissue which enable certain identification and marking of said lesion which is clear, lasting, visible to the naked eye and which can be detected by any imaging method.

According to a first aspect of the present invention a method is provided for identifying and indicating a non-palpable lesion in soft tissue comprising inserting a hollow needle

into said soft tissue, identifying the position of the needle in said soft tissue, further inserting said needle until the tip of the needle reaches said lesion, extracting the needle from said soft tissue, injecting marker means, during said extraction, characterised in that said marker means comprise a macromolecular substance detectable by echography or magnetic resonance.

According to another aspect of the present invention means for identifying and indicating a non-palpable lesion in soft tissue are provided, comprising marker means injectable into said soft tissue along a route leading to said lesion, characterised in that said marker means comprise a macromolecular substance detectable by echography or magnetic resonance. The marker means can also comprise a colouring substance such as active carbon and/or contrast means which can be detected by radiological examination.

Owing to the invention, a durable trace is left along the route of the needle through the tissue to the zone affected by the lesion, in particular due to the presence of the colouring means and the macromolecular substance, said trace being detectable both by the naked eye and by all imaging methods.

According to a further aspect of the present invention a needle usable for identifying and indicating a non-palpable lesion in soft tissue is provided, comprising an internally hollow cylindrical body, characterised in that said hollow cylindrical body ends in a tip which is releasably connected to the hollow cylindrical body and is provided with fixing means suitable for being fixed onto said soft tissue.

The needle according to the invention significantly facilitates execution of the so-called sentinel lymph node technique which is used in surgical interventions on breast tumours in women. This technique consists of injecting, before the surgical intervention, contrast means which can be detected radiologically, for example a Tecnezio solution, on

the tumour lesion to identify, by means of a mammoscintigraphy, the axillary lymph node through which the tumour is drained. After identifying the lymph node, the surgeon removes it so that it can be analysed in order to identify the type of tumour and to decide whether the other axillary lymph nodes have to be removed too.

This technique thus requires the previously identified breast lesion to be located afresh on the day of the surgical intervention so that the radiological contrast means can injected into said breast lesion. This causes the patient physical discomfort and requires close coordination between the departments of Nuclear Medicine, Radiology and Surgery.

The use of the needle according to the invention enables the removable tip of the needle to be left inside the lesion when the breast lesion is identified because when the needle is removed from the patient's body the tip has been positioned inside said lesion and the fixing means of the tip of the needle ensure that the tip remains fixed to the tissue and detaches itself from the needle when the needle is extracted, said tip thus remains inside the patient's body at the identified lesion and thus acts as an accurate reference for injection of the radiological contrast means when the sentinel lymph node technique is carried out.

The invention will be now described hereinafter, in a mere exemplifying and not restrictive way, with reference to the enclosed drawings, in which:

Figure 1 is a longitudinal schematic section of a needle according to the invention:

Figure 2 is a section like the one of Figure 1, which shows the tip detached from the body of the needle;

Figure 3 is a section like the one of Figure 2, which shows a variation of the needle according to the invention;

Figure 4 is a longitudinal schematic section like the one of Figure 1, which shows a construction variation of the tip of the needle according to the invention;

Figure 5 is a section like the one of Figure 4, which shows the tip detached from the body of the needle;

Figure 6 is a section like the one of Figure 3 which shows the application of said construction variation of the tip of the needle to the variation of the needle shown in Figure 3.

The method for identifying and indicating a non-palpable lesion in soft tissue according to the invention comprises inserting a hollow needle into said soft tissue, identifying the position of the needle in said soft tissue, further inserting said needle until the tip of the needle reaches said lesion, extracting the needle from said soft tissue, during said extracting the needle, injecting marker means which comprise a macromolecular substance detectable by echography or magnetic resonance. The macromolecular substance is preferably a synthetic human albumen. The colouring means may be sterile carbon. The marker means may also comprise contrast means which can be detected radiologically.

The use of a macromolecular substance in said marker means, possibly in conjunction with a colouring substance and contrast means which can be detected radiologically, enables certain identification of the route which the surgeon has to follow to reach said lesion. The macromolecular substance in fact leaves a durable trace along the route of the needle inserted as far as the zone of said lesion, which trace can easily be detected by imaging methods such as echography and magnetic resonance. Moreover, if the macromolecular substance is combined with colouring means, said route can be easily seen, also because the macromolecular substance facilitates the persistence of the colouring substance along said route. Finally, if said marker means also comprise contrasting means

which can be detected radiologically said route can, if necessary, be detected by a radiological examination.

In Figures 1 to 6 a needle is shown which can be used to carry out the method according to the invention and which is particularly suitable for performing the sentinel lymph node technique, described above.

In Figure 1, the reference 1 indicates the hollow cylindrical body of the needle according to the invention ending in a tip 2 comprising a shank 3 suitable for being inserted into the cavity 4 of the cylindrical body 1. The shank 3 comprises a cavity 5, communicating, at one end thereof, with the cavity 4 of the cylindrical body 1 and, at the other end, with the inside of the tip 2, said tip being also hollow. The tip 2 comprises holes 6 which enable the hollow interior of the tip 2 to communicate with the exterior. The tip 2 also has fixing means comprising elastic tabs 7 which are connected at one end thereof to the side surface of the tip 2. When the needle is inserted into soft tissue inside the patient's body the elastic tabs 7 are compressed by said tissue against the side surface of the tip 2 of the needle. When the needle is extracted from the patient's body the tabs 7 fix onto the surrounding tissue and are spread out towards the exterior to prevent the tip 2 from being extracted together with the needle. The shank 5 of the tip 2 is extracted from the cavity 4 of the cylindrical body 1 and the tip 2 separates from the cylindrical body 1 and remains trapped inside the patient's body in the position in which it was inserted.

In Figure 3 a variation of the needle according to the invention is shown, in which a tube 8, preferably in radioopaque material, is associated to the shank 5 of the tip 2. When the body 1 of the needle is extracted from the patient's body the tube 8 remains fixed to the tip 2 of the needle. The length of the tube 8 is such that after the body 1 of the needle has been extracted from the patient's body an

end of the tube 8 protrudes and can be used to inject, for example, contrast means which can be detected radiologically for performing the sentinel lymph node technique, at the tumour lesion in which the tip 2 of the needle has been inserted.

The tip 2 of the needle is preferably made with biologically compatible material, i.e. with a material which does not cause undesirable irritations or allergic reactions with the patient's tissues; e.g. the tip 2 of the needle can be made from a titanium steel alloy known under the commercial name "Nitinol" or from AINSI 304 biocompatible steel alloy.

In Figures 4, 5 and 6 a construction variation of the tip 2a of the needle is shown.

According to this construction variation, the internally hollow tip 2a has elastic tabs 7a which are fixed at one end thereof to the base of the tip 2a. Inserting the elastic tabs 7a in the cavity 4 of the body 1 of the needle makes the elastic tabs 7a press against the internal surface of the cavity 4 and thereby anchors tip 2a to the body 1 of the needle. Like tip 2, tip 2a has holes 6, which enable the hollow interior of the tip 2 to communicate with the exterior. After the needle has been inserted into the patient's body, the tip 2a can be released from the body 1 by pushing the tip 2a out of the body 1 through pusher means (not shown) insertable into said cavity 4. Owing to the thrust exerted on the tip 2a by said pushing means the tabs 7 protrude from the cavity 4 and elastically separate as shown in Figure 4 so anchoring the tip 2a to the surrounding tissue.

In Figure 6 a needle according to the invention is shown having a tip 2a, to the base of which a tube 8 in radioopaque material is fixed as already described with reference to Figure 3. The tube 8 communicates with the hollow interior of the tip 2a and can also be used as a pusher to separate the

tip 2a from the body 1 of the needle, after the latter has been inserted into the body of the patient.

The needle according to the invention can also be used, as it has already been said, to mark the route for reaching the tumour lesion. In this case, after the tip 2, 2a of the needle inserted into the patient's body has reached the zone affected by the tumour lesion, extraction of the body 1 of the needle is started and simultaneously the marker means are injected according to the invention. Alternatively, said marker means can also be injected through a common hypodermic needle after the tip of the needle has reached the tumour lesion and during extraction of the needle.

In practice, materials, dimensions and details of execution may be different from, but technically equivalent to those described without departing from the scope of the present invention.

CLAIMS

1. Method for identifying and indicating a non-palpable lesion in soft tissue comprising inserting needle means into said soft tissue, identifying the position of said needle means in said soft tissue, further inserting said needle means into said soft tissue until one tip thereof reaches said lesion, extracting said needle means from said soft tissue injecting marker means during said extracting, characterised in that said marker means comprise a macromolecular substance detectable by echography or magnetic resonance.

2. Method according to claim 1, wherein said macromolecular substance comprises synthetic human albumen.

3. Method according to claim 1, or 2, wherein said marker means comprise colouring means.

4. Method according to claim 3, wherein said colouring means are sterile carbon.

5. Method according to one of claims 1 to 4, wherein said marker means further comprise contrast means detectable by radiological examination.

6. Means for identifying and indicating a non-palpable lesion in soft tissue comprising marker means injectable into said soft tissue along a route which leads to said lesion, characterised in that said marker means comprise a macromolecular substance detectable by echography or magnetic resonance.

7. Means according to claim 6, wherein said macromolecular substance comprises synthetic human albumen.

8. Means according to claims 6, or 7, wherein said marker means comprise colouring means.

9. Means according to claim 8, wherein said colouring means are sterile carbon.

10. Means according to one of claims 6 to 9, wherein said marker means further comprise contrast means detectable by radiological examination.

11. Means for identifying and indicating a non-palpable lesion in soft tissue comprising needle means suitable for being inserted into said soft tissue said needle means comprising a hollow cylindrical body (1), characterised in that said needle means further comprise a tip (2; 2a) releasably fixed to one end of said body (1) and provided with fixing means (7) suitable for fixing into said soft tissue.

12. Means according to claim 11, wherein said tip (2; 2a) is provided with a shank (3) insertable into a cavity (4) of said body (1).

13. Means according to claim 12, wherein said shank (3) is provided with a longitudinal through cavity (5).

14. Means according to claim 13, wherein said tip (2; 2a) is provided with an internal cavity.

15. Means according to claim 14, wherein said internal cavity communicates with said through longitudinal cavity (5) of said shank (3).

16. Means according to claims 14, or 15, wherein said tip (2; 2a) has holes (6) communicating with said internal cavity.

17. Means according to one of claims 11 to 16, wherein said fixing means comprise elastically deformable tab means (7).

18. Means according to claim 17, wherein said tab means (7) are fixed at one end thereof to the external surface of said tip (2; 2a).

19. Means according to claim 17, wherein said tab means (7) are fixed at one end thereof to the base of said tip (2; 2a).

20. Means according to one of claims 11 to 19, wherein said tip (2; 2a) is connected to tubular means (8) insertable into said cavity (4) of said body (1).

21. Means according to claim 20, wherein said tubular means (8) have an end communicating with said longitudinal cavity (5).

22. Means according to claim 21, wherein said end is inserted into said longitudinal cavity (5).

23. Means according to claim 20, wherein said tubular means (8) are fixed at one end of the base of said tip (2a) and communicate with the internal cavity of said tip (2a).

24. Means according to one of claims 20 to 23, wherein said tubular means have a greater length than the length of said body (1) and have a lesser diameter than the internal diameter of said hollow cylindrical body (1).

25. Means according to one of claims 11 to 24, wherein said tip (2; 2a) is made from biocompatible material.

26. Means according to claim 25, wherein said biocompatible material is a titanium steel alloy.

27. Means according to claim 25, wherein said biocompatible material is an AINSI 304 steel alloy.

INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/IB 02/00926

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 44 03 789 A (SCHERING AG) 10 August 1995 (1995-08-10) column 1, line 17-39 column 2, line 6-23 column 3, line 6-25,55-63 column 4, line 33-48 column 5, line 17-26 column 7, line 37-45 ---	6-10
X	US 5 517 993 A (WU GUANLI ET AL) 21 May 1996 (1996-05-21) column 1, line 16-18; claim 1 column 8, line 65 -column 9, line 3 column 12, line 55-60 --- -/--	6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2002	16/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Reinbold, F

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 02/00926

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 08208 A (BIOPSYS MEDICAL INC) 21 March 1996 (1996-03-21) page 1, line 1-4 page 8, line 2-6 page 9, line 14-22	11,17, 25-27
A	page 18, line 2 -page 21, line 24; figures 12-15	12,14, 16-20, 23-27

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/00926

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-5
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IB 02 /00926

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 6-10

   Means for identifying a lesion in soft tissue comprising an injectable macromolecular tracking substance.

2. Claims: 11-27

   Means for identifying a lesion in soft tissue comprising a needle means with a detachable marker tip to be fixed in said tissue.

INTERNATIONAL SEARCH REPORT

....ormation on patent family members

Inte ...al Application No
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(54) Title: TISSUE MARKING USING BIOCOMPATIBLE MICROPARTICLES

(57) Abstract: Described are methods of tissue marking using microparticles that have carbon surfaces, and that contain a contrast agent. Preferred microparticles include a permanently radiopaque particle substrate and a pyrolytic carbon surface.

TISSUE MARKING USING BIOCOMPATIBLE MICROPARTICLES

Background

Tissue marking is a method of marking a site or position in a body to allow re-visiting of the position at a later time to check for progress or developments of an ailment or a treatment or to allow re-treatment at the same site. Tissue marking may be used during biopsy or other tissue-removal procedures to accurately mark the site of the tissue-removal or biopsy in order to allow a treatment-giver to later return to the same site if desired.

Such tissue marking may be useful in procedures relating to colon or rectum biopsies or tissue removal, prostrate biopsies, or breast biopsies. Specifically with respect to breast biopsies, it is not uncommon in modern breast biopsies for all evidence of a lesion to be removed during biopsy. Removing all trace of the tissue also removes identifying features from the site and makes it difficult to return to the same location later to re-check the site. This dilemma, created by a removal of a potentially malignant breast mass or cluster of microcalcifications during core biopsy, can be ameliorated by placing radiographically visible markers immediately after the biopsy. The marker can be used to help locate the biopsy site in case malignancy is determined even if the mammographic findings associated with the original lesions were removed completely.

One localization or marking method involves placing a metallic clip (e.g., a clip sold under the trade name Micromark™, from Biopsys Medical) through an 11- or 14-gauge probe of a biopsy device and attaching the clip to the site of a biopsy to mark the location of the biopsy. These clips are approximately 3mm across and are permanent and radiopaque. The use of marking clips has been described by Burbank et. al., "Tissue Marking Clip for Stereotactic Breast Biopsy: Initial Placement Accuracy, Long-term Stability, and Usefulness as a Guide for Wire Localization," Radiology 1997; 205:407-415; and Liberman et. al., "Clip Placement After Stereotactic Vacuum-Assisted Breast Biopsy," Radiology, 1997; 205:417-422.

Another example of an application for tissue marking is in prostate biopsies. It is recognized that initial biopsies may not be fully determinative in the prostate. See Jonathan I., "Are You Getting Maximum Diagnostic and Prognostic Information from your Prostate Needle Biopsy?" Contemporary Urology, 106, April 1999. Tissue

marking can ensure that the tissue of non-determinative initial biopsies can be monitored for progressive disease and that, if necessary, a follow-up biopsy can be performed at the site of the initial biopsy.

Other methods of tissue marking or localization are described in Fajardo et. al., "Placement of Endovascular Embolization Microcoils to Localize the Site of Breast Lesions Removal at Sterotactic Core Biopsy," Radiology, 1998, 206: 275-278, Goldberg et. al., "Preoperative Localization of Non-Palpable Breast Lesions Using a Wire Marker and Perforated Mammographic Grid," Radiology 146: 833-835, March 1983 and United States Patents 4,341,220 and 5,665,092.

Summary of the Invention

The invention provides a method of tissue marking. The method includes the use of detectable, preferably radiopaque particles delivered to a tissue site for later detection. The particles can preferably be delivered into the body to a desired site by injection using a hypodermic needle and syringe, or another similar instrument, or percutaneously with the assistance of a biopsy probe. Microparticles can preferably be of an average size in the range from about 100 to 1000 microns, more preferably from about 200 to 500 microns, and most preferably from about 251 to about 300 microns, in transverse, cross-sectional dimension. The microparticles can preferably be permanently radiopaque and may optionally comprise a carbon coating.

An optional carbon surface can be coated onto a particle substrate as a thin coating or film, thereby creating a particle having a highly biocompatible carbon surface. While not required, pyrolytic carbon may be preferred.

The particle substrate can be, but is not necessarily, biocompatible and should be capable of withstanding the conditions of a process for coating a carbon surface onto the substrate, which might include elevated temperatures. In particularly preferred embodiments, particle substrates can be radiopaque, most preferably permanently radiopaque. Exemplary radiopaque materials can include metals and metal oxides such as zirconium oxide and aluminum oxide, gold, titanium, silver, stainless steel, oxides and alloys thereof.

The microparticles can be delivered using a fluid carrier which can be any biologically compatible material capable of delivering the microparticles to a desired

tissue site, such as a biologically compatible suspension, solution, or other form of a fluid or gel. Examples of materials useful in biologically compatible carriers include saline, dextrans, glycerol, polyethylene glycol, corn oil or safflower, other polysaccharides or biocompatible polymers, methyl cellulose, glucan, agarose, either singly or in combination.

The use of microparticles in tissue marking methods, preferably by injecting through a hypodermic needle and syringe or a like instrument, has advantages over other tissue marking methods. For instance, delivery of microparticles using a needle and syringe allows very precise delivery of microparticle markers to a desired tissue site; this is particularly true if a biopsy probe used to perform a biopsy is used to assist delivery of microparticles for tissue marking, without first moving the biopsy sheath. Additionally, microparticles can be used in tissue locations where other types of tissue markers are not or cannot be used. For example, some tissue locations such as the colon or rectum do not lend themselves to the use of marking clips, yet it is possible to deliver microparticles to these locations for effective marking. Further, preferred embodiments of the microparticles can be permanently radiopaque. The location of permanently radiopaque particles can be monitored, by known methods, for as long as the radiopaque microparticles remain in a body.

For purposes of the present disclosure, the following terms shall be given the following meanings.

The term "biocompatible," refers to materials which, in the amount employed, are non-toxic and substantially non-immunogenic when used internally in a patient and which are substantially insoluble in blood. Suitable biocompatible materials include ceramics, metals and metal oxides such as titanium, gold, silver, stainless steel, oxides thereof, aluminum oxide, zirconium oxide or carbon such as pyrolytic, low temperature or ultra low temperature isotropic carbon.

The term "detectable" refers to materials capable of being detected during or after injection into a patient by methods generally used for monitoring and detecting such materials, such as magnetic resonance, X-ray, ultrasound, magnetotomography, electrical impedance imaging, light imaging (e.g. confocal microscopy and fluorescence imaging) and nuclear imaging (e.g. scintigraphy, SPECT and PET). Examples include contrast-enhancing agents such as radiopaque materials. Contrast-

enhancing agents may be either water soluble or water insoluble. Examples of water soluble radiopaque materials include metrizamide, iopamidol, iothalamate sodium, iodomide sodium, and meglumine. Examples of water insoluble radiopaque materials include metals and metal oxides.

Detailed Description

The invention provides methods of marking tissue for any reason, such as to mark the site of the removal of a tissue (removal of a polyp from a colon or rectum); to mark the site of a biopsy (a breast biopsy, a prostate biopsy, a colon biopsy, or a rectum biopsy); or to mark the site of any other medical procedure. The tissue may be marked to return to the same tissue site to monitor the progress of a medical condition or a treatment, or to perform a subsequent biopsy at the same site. In addition, detectable microparticles can be delivered to a tissue site to act as a target at which or near a beam of radiation can be precisely directed.

The invention involves marking a tissue site using detectable microparticles, preferably that are also biocompatible. The microparticles contain some detectable component (some well-known detectable components are referred to as a "contrast-enhancing agent") that causes the microparticles to be tracked, monitored, or otherwise detected by known methods, including radiography or fluoroscopy. The detectable component can be any material capable of enhancing contrast in a desired imaging modality (e.g. magnetic resonance, X-ray, ultrasound, magnetotomography, electrical impedance imaging, light imaging (e.g. confocal microscopy and fluorescence imaging) and nuclear imaging (e.g. scintigraphy, SPECT and PET)). Contrast-enhancing agents are well known in the medical arts, with any of a variety of such contrast-enhancing agents being suitable for use according to the methods of the invention.

A detectable component is preferably capable of being substantially immobilized within a microparticle, and may be incorporated into a microparticle for use in tissue marking in any of a variety of ways, such as part of a particle substrate, as a surface coating, as an additive to a surface coating such as a carbon coating, or elsewhere. A detectable component can be added to a material that is not radiopaque.

The detectable component may be provided in any location or portion of a microparticle by known methods.

According to an embodiment of the invention, the microparticles comprise a permanently radiopaque material which can be detected within a body following delivery to a tissue site. Permanent radiopacity is unlike contrast-enhancing agents or radiopaque materials which biodegrade or otherwise lose their effectiveness (detectability or radiopacity) over a period of days or weeks, such as 7 to 14 days. An advantage of permanent radiopaque materials is that they can be detected for as long as they remain in a body, whereas non-permanent radiopaque materials or other types of contrast-enhancing agents are detectable for only a limited time. See copending United States Patent Application Serial Number 09/602,323, entitled Embolization Using Carbon Coated Microparticles, and filed on June 23, 2000.

Some examples of radiopaque materials include paramagnetic materials (e.g. persistent free radicals) and compounds, salts, and complexes of paramagnetic metals (for example transition metal or lanthanide ions); heavy atom compounds (i.e. atomic number of 37 or more) salts, or complexes (e.g. heavy metal compounds, iodinated compounds, etc.); radionuclide-containing compounds, salts, or complexes (e.g. salts, compounds or complexes of radioactive metal isotopes or radiodinated organic compounds); and superparamagentic materials (e.g. metal oxide or mixed oxide particles, particularly iron oxides). Paramagnetic metals include Gd (III), Dy (III), Fe (II), Fe (III), Mn (III) and Ho (III), and paramagnetic Ni, Co and Eu. Heavy metals include Pb, Ba, Ag, Au, W, Cu, Bi and lanthanides such as Gd.

The amount of detectable material included in a microparticle used for tissue marking should be sufficient to allow detection of the microparticle as desired. The amount used in any particular application or microparticle may depend on various factors such as the size of the microparticles, the total amount of microparticles delivered, the type of contrast-enhancing agent, etc. According to some embodiments of the invention, microparticles can be made up of 100 percent radiopaque material. Alternatively, for radiopaque particles that are coated with a carbon surface, the microparticles can have any relative amounts of radiopaque particle substrate to carbon coating that will allow the microparticles to be used as detectable tissue markers, for example from about 50 to 100 percent by weight radiopaque particle substrate based

on the total weight of the particle substrate and the carbon coating. Optionally, some, i.e., only a portion, but not all microparticles used in a particular tissue marking procedure (tissue marking composition, as described below) can include a detectable component.

In one embodiment of the invention, the microparticles are completely made up of permanently radiopaque material, in a form that is biologically compatible, and are delivered directly to a tissue site as such.

In another embodiment, microparticles for tissue marking according to the invention can have a surface that comprises carbon. The carbon-containing particle surface may be in the form of a carbon-containing coating or carbon-containing film of any type of carbon, e.g., pyrolytic carbon such as low temperature isotropic (LTI) carbon, another type of isotropic carbon, or vitreous carbon, preferably in a form that is biocompatible. Various forms of carbon are described in Beavan, "Material Properties and Applications of Pyrolite® Carbon," Materials Engineering, February 1990. Examples of carbon coated particles are described in United States Patent 5,792,478.

The atomic structure of both pyrolytic carbon and vitreous carbon is similar to graphite, a common form of carbon, but the alignment between hexagonal planes of atoms is not as well ordered as in graphite. Pyrolytic carbon is characterized by a more chaotic atomic structure with warped hexagonal planes, missing atoms, and generally a more turbostatic appearance. This results in better bonding between layer planes.

The carbon coated microparticles can be constructed as a particle substrate having a carbon surface. While the substrate need not be biocompatible due to its being coated with a biocompatible layer comprising carbon, it can be preferred that the particle substrate may also be biocompatible.

Such carbon coated microparticles may be prepared using any of a variety of coating processes to deposit carbon onto a particle substrate. A particle substrate can be selected for compatibility with the coating process, meaning that it should be capable of withstanding temperatures used in a given process for coating carbon onto a particle substrate. Relatively hard metallic or ceramic materials capable of withstanding high temperature conditions of a coating process are generally preferred materials for a particle substrate. Metals, metal oxides, and alloys, including but not limited to medical grade stainless steel, silver, gold, titanium and titanium alloys, and

oxide derivatives of stainless steel or titanium or titanium alloys, are also acceptable materials for the particle substrate, with aluminum oxide and zirconium oxide being especially suitable. Carbon itself in any of its various forms, such as pyrolytic carbon, non-pyrolytic carbon, isotropic carbon, graphite, or vitreous carbon, may be useful as a particle substrate material. Thus, the microparticles may include a carbon coating deposited on a carbon particle substrate, and may be substantially or entirely made of carbon. In one embodiment of the invention, both the particle substrate and the carbon coating may comprise pyrolytic carbon.

Particle substrates intended to be coated with carbon, whatever their composition, should be of sufficient diameter, shape, and uniformity that they can be coated with carbon to produce carbon coated particles of a size, quality, and nature as described herein. Preferably, the particle substrates, prior to coating, can be selected and milled, extruded, sifted, cleaned, filtered, or otherwise formed to provide a desired combination of particle size, shape, and quality, to result in coated particles of a desired size, shape, and quality.

Pyrolytic carbon can be produced and coated onto a substrate surface by known methods. Generally, hydrocarbons and alloying gases are decomposed to prepare a pyrolytic carbon coating on a particle substrate. The particle substrates are included with the hydrocarbons and alloying gases in a fluidized or floating bed at a temperature sufficient to cause deposition of pyrolyzed carbon onto the substrate surface, typically from about 1200 to 1500°. Inert gas flow is used to float the bed of particle substrates, optionally including an inert mixing media. The hydrocarbon pyrolysis results in a high carbon, low hydrogen content carbon material being deposited as a solid material onto the particle substrates.

Alternatively, a carbon coating (sometimes referred to as "ultra-low-temperature isotropic carbon") may be applied to a particle substrate using any one of other various coating processes for depositing carbon, such as a vacuum vapor deposition process. Such a method uses ion beams generated from any of a variety of known processes, such as the disassociation of CO_2, reactive dissociation in vacuum of a hydrocarbon as a result of a glow discharge, sublimation of a solid graphite source, or cathode sputtering of a graphite source. Gold has been found to be an especially suitable substrate material for vacuum vapor deposited carbon. Other substrates,

including but not limited to nickel, silver, stainless steel, or titanium are also quite acceptable as a substrate material for this type of coating process.

The high strength, resistance to breakdown or corrosion, and durability of a carbon surface ensures effective, long term functioning of microparticles in tissue marking applications. The established biocompatibility of carbons such as pyrolytic and vitreous carbon makes the described particles particularly suitable for tissue marking applications. The microparticle substrates may be completely encased by a carbon surface. This results in a smooth coated particle with no substrate exposure on the surface of the particle. Preferred carbon coatings can be in the range of fractions of thousandths of an inch, e.g., about one half of a thousands of an inch (0.0005 inches), on average, covering the surface of the particle substrate.

The microparticles, whether coated or uncoated, are preferably generally rounded particles that have a smooth surface. The smooth surface enhances passage of the microparticles through a hypodermic needle. Microparticles are preferably subjected to a cleaning and sieving process to remove contaminants and to separate out particles of a size less than or greater than a desired size range. The particles may preferably range in size from 100 microns to 1,000 microns in average, transverse cross-sectional dimension, preferably in the range from about 200 to 500 microns, and a particularly preferred size range for use in tissue marking applications can be between about 251 and about 300 microns. To achieve this most preferred such size range, microparticles may be segregated to a selected size range, for example using a sieving process such that the minimum microparticle dimension will pass through a U.S. No. 50 Screen Mesh (300 micron grid size opening) but will not pass through a U.S. No. 60 Screen Mesh (250 micron grid size). That minimum dimension will be the transverse, cross-sectional dimension on oblong or elongated particles, with that dimension coinciding with the particle diameter on generally spherical particles.

Microparticles can be delivered to a tissue site using any instrument or apparatus that can be used to inject an amount of microparticles, preferably contained or suspended in a carrier, through the skin, mucosa, or through an incision in the skin, to a desired tissue site. Preferred instruments include instruments such as hypodermic needles or other similar needle-like apparatuses, such as any small bore instrument, cannula, etc. (All of these types of instruments will be referred to collectively herein,

for convenience, using the term "hypodermic needle" or "needle.") The particular instrument used for delivery is not critical, provided that its components are compatible with the tissue marking composition.

According to one example of a method of delivering microparticles for tissue marking, microparticles can be delivered using a hypodermic needle and a syringe, by inserting the hypodermic needle into a desired tissue site, followed by delivery of the microparticles to the tissue site.

Optionally, any of a variety of surgical or non-invasive or minimally-invasive surgical instruments can also be used to assist in delivery. For example, following removal of a polyp from a colon or a rectum, by known surgical methods, a hypodermic needle can be inserted through the mucosa at the site of the polyp to deliver microparticles. As another example, a mammotone inserted through a small incision in the skin can be maintained in the operative position and a needle can be inserted through its sheath, to precisely deliver microparticles to the site of biopsy.

Once a needle is placed, microparticles can be slowly injected through the needle to the desired tissue site. The microparticles are of a size that can be effectively deposited through a hypodermic needle or like instrument, and that will substantially remain at the tissue site where delivered. If the particles are too small, they can be engulfed by the body's white cells (phagocytes) and carried to distant organs or be carried away in the microvasculature and travel until they reach a site of sufficient constriction to prevent further movement. On the other hand, particles should not be so large that they cannot be effectively delivered using a hypodermic needle or the like. For the method of the present invention, a particularly preferred, average microparticle size can be from about 100 to 1000 microns, alternatively from about 200 to 500 microns or from about 251 to 300 microns, because such sizes can allow injection through small bore instruments and are small enough to avoid migration of the microparticles from the injection site.

The use of microparticles in tissue marking methods, preferably injected by use of a needle and syringe or a like instrument, has advantages over the use of other tissue marking methods. For instance, delivery of microparticles using a needle and syringe allows very precise delivery of microparticles to a desired tissue site. This is particularly true if the biopsy probe used to perform a biopsy is used to delivery the

microparticles, without first moving the probe sheath. Other advantages are that microparticles can be used where other types of tissue markers either cannot be, or are not used. Specifically, tissue-marking clips are not used in the colon or rectum, but microparticles can be injected to these tissues. Additionally, tissue marking clips can sometimes be inadvertently attached to tissue that will move and cause movement of the clip, such as a ligament. The injection of microparticles avoids such problems.

The amount of microparticles introduced in a tissue marking procedure can be any amount sufficient to mark a location to be detected at a later time. The amount delivered can vary depending on factors such as the size of the microparticles the amount of detectable component in the microparticles factors relating to the patient, etc. Such factors will be within the skill of an artisan of ordinary skill in the medical or tissue marking arts, and such an artisan will be able to understand what is a useful amount of microparticles for delivery to body tissue sites.

According to the invention, the microparticles can be contained and used for delivery in a tissue marking composition comprising an injectable combination of microparticles in a biocompatible carrier. The carrier can be any biocompatible fluid capable of delivering the microparticles to a desired tissue site. A carrier may include, a biologically compatible suspension, solution, or other form of a fluid or gel. Examples of materials useful in biologically compatible carriers include saline, dextrans, glycerol, polyethylene glycol, corn oil or safflower oil, other polysaccharides or biocompatible polymers, methyl cellulose, glucan, agarose, either singly or in combination.

The carrier can preferably be an aqueous suspension or solution, other fluid, or gel of polymeric chains of B-D glucose, commonly referred to as β-glucan. The glucose units are linked to each other at the 1-3, 1-4, or 1-6 positions and form polymeric chains ranging to several thousand daltons in weight.

β-glucan is a naturally occurring constituent of cell walls in essentially all living systems including plants, yeast, bacteria, and mammalian systems. Its effects and modulating actions on living systems have been reported by Abel et. al., "Stimulation of Human Monocyte B-glucan Receptors by Glucan Particles Induces Production of TNF-∂ and 1L-B," Int. J. Immunopharmacol., 14(8):1363-1373, 1992. β-glucan, when administered in experimental studies, elicits and augments host

defense mechanisms including the steps required to promote healing by first intent, thereby stimulating the reparative processes in the host system. β-glucan is removed from tissue sites through macrophagic phagocytosis or by enzymatic destruction by serous enzymes. The destruction or removal of β-glucan, as well as its available viscosity and lubricous nature, make it a useful carrier for the microparticles in tissue marking applications.

Aqueous solutions, suspension, fluids, or gels of β-glucan can be produced that have favorable physical characteristics as a carrier for microparticles in tissue marking applications. The viscosity can vary from a thin liquid to a firm, self-supporting gel. Irrespective of viscosity, the β-glucan has excellent lubricity, thereby creating a particle-carrier composition which is easily administered by delivery to a predetermined body site through a small bore needle. A useful β-glucan composition is β-D-glucan containing 4-0-linked-β-D-glycopyranosyl units and 3-0-linked-β-D-glycopyranosyl units. The carrier can be of sufficient viscosity to assure that the microparticles remain suspended therein, for a sufficient time duration to accomplish the injection procedure.

Another example of a carrier material is methyl cellulose or another linear unbranched polysaccharide. Further examples of appropriate carrier materials include agarose, hyaluronic acid, polyvinyl pyrrolidone or a hydrogel derivative thereof, dextran or a hydrogel derivative thereof, glycerol, polyethylene glycol, succinylated collagen, liquid collagen, oil-based emulsions such as corn or safflower, or other polysaccharides or biocompatible organic polymers either singly or in combination with one or more of the above-referenced solutions.

The amount of microparticles to carrier in a tissue marking composition can be any amount that will provide a tissue marking composition that is flowable and injectable, and that will allow a desired amount of microparticles to be delivered to a tissue site. Amounts of microparticles in a tissue marking composition can be in the range from about 20 to 60 percent by volume or from about 25 to 40 percent by volume.

In use, the tissue marking composition can typically be injected as a slurry, suspension, or emulsion, through a needle, into a body tissue site. When deposited into a body tissue, the carrier will be carried away into the body and disperse or be

destroyed. It is necessary that at least some of the microparticles, preferably most or substantially all of the microparticles, are substantially immobile upon deliver to a tissue site for marking. Microparticles used for tissue marking according to the invention are sufficiently immobile to be used for tissue marking applications. If the microparticles tend to move at all after delivery to a tissue site, the microparticles generally will do so only up the path of the needle used to inject them.

While subsequent portions of the description include language relating specifically to tissue marking in breast biopsy applications, all types of tissue marking applications are considered to be within the contemplation of the present invention. Examples include other types of biopsy applications such as colon, rectum, or prostate biopsies, and non-biopsy applications including tissue marking for other types of medical procedures. The tissue may also be marked to provide a target at which a beam of radiation can be precisely directed. One of ordinary skill in the medical or biopsy arts will understand and appreciate how detectable microparticles can be used in these and other tissue marking or biopsy processes.

Factors that might be considered, controlled, or adjusted for in applying the process to a particular tissue marking application might include consideration of the composition of the microparticles; the amount of microparticles to be delivered to the body site; factors relating to the method of delivery including the particular equipment (a needle or biopsy probe) used for delivery, and the method and route used to place the dispensing end of the delivery device at the desired body site. All of these factors will be appreciated by one of ordinary skill in the tissue marking or medical arts, and can be readily dealt with to apply the described methods to a wide variety of tissue marking procedures.

Biopsy is a method by which a tissue sample is removed from a site of a body to diagnose the tissue as healthy or diseased. Biopsies are performed on tissues of many different body organs, including prostate and breast tissues. The means used to perform the biopsy can include any equipment and techniques generally known or useful in biopsy procedures.

Breast biopsies can be performed using stereotactic, vacuum-assisted breast biopsy techniques and equipment therefore. Such techniques and equipment involve the use of minimally invasive instruments and techniques such as automated surgical